20 September, 2004

Division of Dockets Management (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, rm. 1061,
Rockville, MD 20852.

Subject: Scientific Considerations Related to Developing Follow-On Protein Products [Docket No. 2004N-0355] August 16, 2004

Dear Madam/Sir:

Pharmaceutical Scientist, Inc is a consulting company with experience in establishing biogeneric manufacturing facilities around the world. We are pleased to offer our comments to the questions asked by the FDA on the issue of "follow-on" protein products based on our hands-on experience and evaluation of the science and technology associated with the manufacturing of recombinant therapeutic protein products.

Given below are the questions raised by the FDA in **bold**; our response follows immediately.

A. Manufacturing Issues

1. What aspects of the manufacturing process determine the characteristics of a protein product whether produced through biotechnology or derived from natural sources?

For naturally derived products, the most important component is the source of tissue, its validation for freedom from adventitious agents, extraction method, in-process controls, validation of unit processes involved, characterization of protein, characterization of impurities, stability profile, formulation including excipients and preservatives, filling, lyophilization (if required) and interaction with container and closure system.

For recombinant products, the most important factor is the genetically modified organism, its DNA sequencing, construction of plasmid and genetic stability of the cell line used. In the upstream processing, the fermentation conditions and control parameters are critical; in the downstream phase, the harvesting and selectivity and specificity of isolation and purification steps (unit operations) are important. Once the drug substance has been obtained in a purified form, the drug product formulation including excipients and preservatives and the validation of filling (including lyophilization, if applicable) and interaction with container and closure systems become important.

The following DOES not always determine the characteristics of a protein product:

1. The starting material. When an innovator develops a GMC, it is one of the several possibilities available, from the choice of cell, the plasmid, the selection of

medium and a variety of other variables. There are myriad possibilities to achieve the same result and it is not necessary to follow the same path to achieve the same result. Obviously, whichever systems is adopted, this must be properly characterized to assure consistency.

2. The process; we have seen growth hormone produced by different GMCs with similar activity and ADR profile. Further, the FDA has scores of Comparability Protocols, attesting to the fact that changes in the manufacturing process at any level is possible without affecting the final identity and quality of the product. The claim by innovators that their long experience in adhering to proprietary in-process controls is critical to the quality and safety of the product is not well-founded. Whereas in-process controls do affect the consistencies in the quality of the product, these controls are not necessarily developed empirically since the stages of production are well defined. During the past two decades, availability of more sensitive, validated methods have allowed improved monitoring of the manufacturing process.
3. The impurity profile of product. Biological products inevitably have impurities, some formed during the storage shelf-life; however, the manufacturing process of therapeutic proteins subjects them to highly efficient purification processes that readily remove many impurities and the level of impurities allowed can be very closely controlled. When FDA approved products two decades ago, many of these purification techniques and/or the monitoring of eluant were not available. As a result, the products manufactured today can be purer that allowed two decades ago. As a result, it is entirely possible for a biogeneric product to have a better impurity profile than the product marketed by the innovator.

2. What parts of the manufacturing process should the agency focus on when assessing similarity between products?

In our experience, the robustness of the cell line used in rDNA production is of critical importance. Appropriate protocols are currently placed at ICH to characterize cell lines and where necessary freedom from adventitious materials; these are adequate. The downstream processing for complicated products such as the glycosylated products, products undergoing refolding, etc., should have appropriate validated in process controls.

B. Characterization

1. What is the capability of current analytical technology to adequately characterize protein products?

The scientific techniques available far exceed their exploitation in the characterization of the final product. There are sufficient tools available to adequately characterize therapeutic proteins in their native state.

2. Are there new technologies that hold promise for helping to characterize proteins?

Yes, CD, 2D NMR and high resolution mass spectra (MS/MS, particularly) should be extensively utilized, where necessary and the choice should be left to the applicant to justify, at least initially, until such time that the USP is able to develop specific monographs.

3. What factors, including quality attributes, impurity profiles, and changes in the manufacturing process, should be considered when assessing similarity of different protein products?

All those elements that the FDA considered necessary in developing its Comparability Protocol requirement should apply to biogeneric products as well.

4. Is it possible to accurately predict safety and efficacy from analytical studies?

There has never been or ever will be any analytic study for any drug, biological or otherwise that will "accurately predict" safety and efficacy. The purpose of using analytical studies is to offer an assurance that the product will be safe and efficacious. These premise apply equally to biological products as well as they do to small molecules.

C. Immunogenicity

1. How, and to what extent, should immunogenicity be evaluated for a follow-on protein product?

Given the statistical probably of immunogenic response, it has never been possible for the FDA to fully evaluate the immunogenicity potential of any new BLA ever approved; the FDA does not require an extended protocol in the Comparability Protocol either; the same standard should apply to biogeneric products. The variables between an innovator product and the biogeneric product are not any more than whatever is allowed in the Comparability Protocol for the innovator. It is remarkable that despite the potential for immunogenic reactions, the marketed products administered to millions of individuals around the world have not reported any unusual ADRs, disproportionate to the extent of their use. It is not possible to evaluate immunogenic potential of any compound using a comparability protocol. The FDA should base its decision on the history of product use. The biogeneric applicant should provide to FDA a detailed history of ADRs reported (if necessary getting through citizen's petition from the innovator and from the databases of regulatory agencies). This is an important consideration since it is well established that subtle differences between batches are inevitable. The fact that the incidence of ADRs has been minimal (vis-à-vis what was feared) attests to the robustness of formulations. More serious concerns should be raised for products which are modified like pegylated products or products where the amino acid sequence has been altered (e.g., Lispro). A compound which is identical to the endogenous product is similarly subject to extensive metabolism in the body and thus immunogenicity; this potential is almost always more important than the immunogenic response due to differences in the formulation (though it has been shown for several drugs). Immunogenicity is a natural process of body to many of body's own proteins; autoimmune disorders are part of the immune system;

comparisons between innovator's product and the biogeneric product for immunogenicity potential is not necessary for most products; however, a limited human study to show possible major differences may be necessary for products where sufficient data exist that subtle differences in formulations can product significant differences in the ADRs.

2. Under what circumstances should comparative immunogenicity studies be conducted?

Only in the case of products known to produce variable immunogenic response; the burden should lie with the applicant to prove otherwise.

D. Preclinical and Clinical

1. When and how would it be appropriate to streamline or eliminate certain animal or human studies during development of a follow-on protein product?

For products with long history of use, and as a result, a long history of reported safety, there is no need to require any animal or human studies. It is clearly established that every batch of every pharmaceutical product, biological or otherwise, is subtly different; a long history of safety of use therefore validates that these subtle differences are not material. The greater the safety profile, the broader is the range of variability admissible. .

E. Potency and Surrogates for Efficacy and Safety

1. What factors should be considered regarding bioactivity and potency assays used for comparing two products?

Some products can be easily tested using established bioassays and for these products the biogeneric manufacturer should employ these methods to establish the efficacy of the product. Several novel methods have recently become available wherein the two products can be compared; much emphasis should be placed in developing these methods.

2. What is the role of in vitro and in vivo assays for use as surrogates in establishing safety and efficacy?

These assays, as allowed in the EP/BP/USP monographs for biological products are the most important tools to establish equivalence. The biogeneric manufacturer should be required to suggest methods that it considers adequate for the purpose until such time that the USP is able to establish specific monographs. However, any additional requirement, over and above appended to the Comparability Protocol would be superfluous.

F. Terminology

1. Please comment on the appropriateness of this notice's working definition of "follow-on protein" as a protein that is intended to be a similar version or copy of an already approved or licensed protein pharmaceutical product.

The word, “follow-on” has specific meaning in the British English usage. For example, in the game of cricket, the Law 13 of the Cricket Board is labeled as: The follow-on. According to this law, the term refers to a lead on first innings wherein (a) In a two innings match of 5 days or more, the side which bats first and leads by at least 200 runs shall have the option of requiring the other side to follow their innings. Many other examples like this show how the word, “follow-on” is used interpreted worldwide. In the US English, the use of “follow-on” has different connotation and is definitely not equivalent to what is generally conceived of the word, “generic.” On the other hand the word, “biogeneric” is widely understood; it does NOT mean equivalent product as demonstrated by the 505 clauses. There is absolutely no need to invent another term, which would be poorly understood and lead to inappropriate differentiation of the biological products from non-biological products.

Now I want to bring to the attention of FDA, an argument that has not been fully brought to light. Why are we talking about giving these products any name other than generic? The word generic is clearly understood by medical profession, any other title would take an insurmountable effort to establish these products professionally, something which is the clear an agenda of the innovator companies.

2. Please comment on this notice's working definition of a “second-generation protein product” as a product similar to an already approved or licensed product but which has been deliberately modified to change one or more of the product's characteristics (e.g., to provide more favorable pharmacokinetic parameters or to decrease immunogenicity).

This is inappropriate, unnecessary and violates the legal meaning of the intent.

We are in unique position to offer additional comments as follows:

1. Millions of people around the world are currently benefiting from biogeneric products; the source of these raw materials is not necessarily in full compliance with the characteristics of the innovatgor’s product. No catastrophes have been reported anywhere in the world; more side effects have been reported when innovators try to change the product formulations without adequate studies.
2. The US FDA has access to the specifications used by the innovators and is thus in a better position to establish the guidelines of Comparability Protocols without compromising the intellectual property involved.
3. The innovators get protection of their inventions under the US Constitution so that at the end of the patent expiry term, mankind can benefit from it. This requires a mandatory disclosure of every detail necessary to manufacture the product. It is true that the patentee need not disclosed whatever is learned afterwards, yet the moral issues of safety to consumers should dictate that the innovators disclose fully to the FDA what is considered critical. It is doubtful that there is a lot to be learned from this exercise given the highly sophisticated techniques that fully

characterize the products; but this would help FDA in establishing better guidelines.

4. The FDA has statutory right as allowed by the case law to approve biogeneric products without any further instructions in the legislature.

We hope you find these comments useful.

Sincerely,

Sarfaraz Niazi

Sarfaraz K. Niazi, Ph.D.
CEO, Pharmaceutical Scientist, Inc
20 Riverside Drive
Deerfield, IL 60015
Phone 847-927-9405 ; fax 312-803-1868
niazi@niazi.com